

Creatine Derivatives: Rapid Complete Relief of Pain by Topical or Transcutaneous Administration

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ABSTRACT

Our research reveals that non-toxic creatine derivatives, especially N-acetyl-creatine ethyl ester, to be therapeutically effective on topical application or by superficial subcutaneous injection over sites of pain to rapidly alleviate or eliminate pain associated with various inflammatory conditions including arthritis, acute common headache, osteoarthritis, psoriatic arthritis, rheumatoid arthritis and various other pains associated with inflammation.

Keywords:

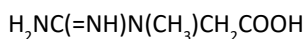
Creatine, Inflammatory, Arthritis, Sprinting, Monohydrate

Introduction

A search for anti-pain molecules was started because both authors personally were developing pain conditions not relieved by available medications.

Creatine is believed to improve strength, increase lean muscle mass and help the muscles recover more quickly during exercise [1-3]. This muscular boost may help athletes achieve bursts of speed and energy, especially during short bouts of high-intensity activities such as weight lifting or sprinting.

Creatine is N-methyl-N-guanylglycine and has the following chemical formula.



Creatine has molecular weight 131 g/mol. One gram of creatine monohydrate dissolves in 75 ml water, about 1.3%, and is practically insoluble in alcohol or other non-aqueous vehicles.

Same as creatine, N-acetyl creatine ethyl ester is a safe compound with LD 50 higher than 400 mg/kg by subcutaneous injection.

Creatine is an amphoteric compound, both positively and negatively charged in aqueous solution. Therefore, creatine cannot readily penetrate human skin, and therefore is not bioavailable for therapeutic effects. Certain creatine derivatives have been claimed to be useful for treatment of diseases of the nervous system [4-7]. We have synthesized various creatine derivatives which are in bioavailable form.

Methods

All the creatine derivatives including N-acetyl-creatine ethyl ester, and N-2 acetoxybenzoyl ethyl ester have been synthesized, purified, and identified by mass spectroscopy and HPLC.

For topical administration, a creatine derivative was typically dissolved in an aqueous solution consisting of water 40 parts, ethanol 40 parts and propylene glycol 20 parts by volume (WEP442) or an anhydrous solution consisting of ethanol 70 parts and propylene glycol 30 parts by volume (EP73).

For example, 4% N-acetyl creatine ethyl ester was formulated

readily as C15 X4 WEP442 for topical application.

Subjects included ourselves, former patients from dermatologic practice seeking our help for their painful conditions, family members and professional associates.

All participants were thoroughly familiar with or were thoroughly instructed in applicable areas of chemistry, metabolism and in what is generally known regarding inflammation and pain.

Presented herein are 17 case reports of pain conditions occurring in 12 patients/subjects relieved by topical and/or subcutaneous administration of a creatine derivative. Topical formulations were provided to patients with instructions to apply to involved areas only for relief of pain, not otherwise. Injections were administered in office.

Results

A creatine derivative, N-acetyl creatine ethyl ester (C15) has been used predominantly against various conditions of pain described in the following clinical case reports.

Effect on acute knee pain

A female, age 43, with a painful left knee due to physical trauma, reinjured the knee while cleaning her house. Degree of pain was sufficiently intense that it required her to wear a knee brace throughout the day. After about one week while shoveling heavy snow and wearing the knee brace she sustained a traumatic twisting of the knee which caused intensified pain of the knee. She was provided a formulation of N-acetyl creatine ethyl ester 1.5% dissolved in water: propylene glycol 8:2 (C15X 1.5 WP82) for topical application. At follow-up 5 days later, she reported that within about 2 minutes after topical application of the formulation to the knee, pain in the knee completely vanished "like a miracle". Pain had not recurred at the time of her report 10 days later. At 2 weeks follow-up visit no pain had returned.

Effect on acute neck pain

A male subject, age 45, who, in the previous day had shoveled heavy snow all day long, throwing the snow mostly to the left, upon arising from bed next morning experienced acute pain in his neck that intensified as he attempted to move his head in any direction. His spouse had in her possession the formulation of N-acetyl creatine ethyl ester 1.5% dissolved in water:

propylene glycol 8:2 that she had topically used the previous day to obliterate pain in her left knee as described above, which formulation she applied to the neck of her husband. Within 2 minutes his neck pain subsided completely and did not return.

Effect on rheumatoid arthritic fingers

A female of age 60, noted changes in her fingers that appeared to be compatible with the diagnosis of early rheumatoid arthritis in autumn of the year. At about one month later there appeared, over the terminal interphalangeal joint of the left third finger, a raised inflammatory nodule compatible with the diagnosis of a rheumatoid nodule. The nodule was injected with 0.15 ml of a 2% aqueous sterile solution/suspension of creatine monohydrate once weekly at four office visits. Thereafter 3 intralesional injections of 1.5% C15 in aqueous solutions were given weekly. Over a period of 9 weeks the nodule resolved almost completely, leaving a faint erythema at the site (Figure 1). Thereafter, for a period of one month she wore a nitrile glove containing a few drops of N-acetyl creatine ethyl ester 3% dissolved in water: propylene glycol 8:2 for about an hour twice daily on the left hand only. Over a period of 9 weeks the nodule resolved almost completely, leaving a faint erythema at the site. After another two months the following benefits had occurred.



Figure 1: Rheumatoid Arthritis (RA). Rheumatoid nodule during intralesional injection with N-acetylcreatine ethyl ester.

The left hand was said to feel much better than the right hand. The site of the nodule remained a slightly erythematous flat macule.

The left hand and fingers were completely flexible; the flexibility of the right hand was restricted. Thereafter subject wore a nitrile glove containing a few drops of C15 9% dissolved in WEP 442 for about an hour twice daily on the left hand only (Figure 2). After another 2 months C15 was topically applied by means of her wearing nitrile gloves containing the C15 solution for about 1 hour twice daily to both hands. After 8 months both hands appeared to be completely normal (Figure 3).

Effect of whole-body application

A male, age 98, with continually worsening very painful osteoarthritis of multiple joints for 15-16 years, prepared the following formulation: N-Acetyl creatine ethyl ester (C15) 2% in Water: Propylene glycol: Mineral Oil: Sodium lauryl sulfate 68:30:0.5:1:0.5. After taking a morning shower, he applied 40 ml of the formulation to his entire body, except the scalp. Within



Figure 2: Rheumatoid arthritis: Right hand (left photo); No treatment; Left hand (right photo), After 4 months of topical treatment with N-acetylcreatine ethyl ester.



Figure 3: Rheumatoid arthritis: Right hand (left photo); After 2 months of topical treatment; Left hand (right photo); After 8 months of topical treatment with N-acetylcreatine ethyl ester.

about 5 minutes all pain ceased in all previously painful joints, i.e. spine, right shoulder, right elbow, knees and feet. Subject was without any sense of pain for 4.5 hours when mild painful discomfort in the neck was sensed. Over the next 3 hours pain in all joints returned to usual substantial levels.

Rapid pain relief and resolution of aphthous ulcer (canker sore) by topical application of N-acetyl creatine ethyl ester (C15)

A painful site 2-3 mm in diameter on the right side of the tongue worsened over 2 days in male, age 98.

At bedtime of the 2nd day C15 3% in water: propylene glycol 8:2 (C15X3WP82) was topically applied to the ulcerated area. Complete pain relief occurred within less than a minute. The sites remained pain free throughout the night and did not return. No clinical sign of the lesion could be detected next day by subject, nor by two associates.

Instant complete relief of pain of thermal burn by topical N-acetyl creatine ethyl ester (C15)

A male age 60, spilled boiling hot water on his left hand. Within a couple hours pain was intense. He then applied 4% solution of N-acetyl creatine ethyl ester (C15) dissolved in water: ethanol:

propylene glycol 4:4:2 which he had been using to relieve pain over a lateral meniscus. He reported there was immediate relief of the burn pain for periods of 4-5 hours. Such application was repeated over the next several days until the burn pain disappeared spontaneously.

A female, age 60, burned a linear site on her left forearm by accidentally touching a hot oven rack. She immediately applied 9% solution of N-acetyl creatine ethyl ester (C15) dissolved in water: ethanol: propylene glycol 4:4:2 that she was using for topical treatment of her rheumatoid arthritis. Burn pain was instantly relieved, lasting for 4-5 hours. Repeated applications were applied over the next 3 days, until burn pain spontaneously ceased.

Pain of dystonia relieved by local subcutaneous injections of N-acetyl creatine ethyl ester (C15), relief lasting for 2-3 weeks

A female, age 59, presented with muscular pain of her upper right back which had been diagnosed by 2 physicians as a symptom of dystonia (which also caused involuntary tic movements of her head). Five sites of the upper right back were each injected with 0.3 ml C15 4% in aqueous solution using insulin syringes with 30 G short needles.

Complete relief of pain occurred within the next hour, such relief lasting for 2 weeks. At that time the injections were repeated just before she departed on a trip to Europe. By phone she reported that relief of pain was lasting beyond a two-week period.

Effects of N-acetyl creatine ethyl ester (C15) on osteoarthritis of various body joints

Elbow: A male subject, age 65, presented with a history of painful right elbow for several weeks. He was provided with a topical solution of C15 8% in WP 82. He reported that application of this solution to the elbow relieved pain instantly and completely, lasting for 5-6 hours.

Another male subject, age 99, with a history of right elbow pain, for several months, applied the above same solution to the elbow multiple times. Minimal pain relief was experienced.

On three occasions C15 1.5% aqueous solution 1 ml was injected subcutaneously in two lateral sites of the elbow and one site over extensor part of the elbow. Such injections provided complete relief of pain within an hour, lasting for 24-30 hours.

Shoulder: The same 99 year old male with painful right shoulder for several months was injected with 1ml of the above solution over the shoulder joint on three occasions. Each provided complete relief of pain lasting for 6-7 days after the first two injections, and not returning for 2 months after the 3rd injection. Thereafter the shoulder developed a dull ache relieved by mild heat.

Spine: The same 99 year old male instructed his assistant on the technique of subcutaneous injections. On four occasions over a period of 3 months subcutaneous injections of 0.6 ml of the above C15 solution were injected subcutaneously into each of 5 intervertebral sites of his cervical and thoracic spine. On each occasion complete relief of pain was experienced; duration of relief lasted variously for 1-4 weeks.

Knees: A 65 year male has reported that a solution of C15, 8% in WP 82 applied to a cotton gauze wrapping of the knees and then occluded with a plastic wrap provided complete relief of pain for 8 hours of night sleep. After removal of the wrapping in the morning, he found that almost complete diminishment of pain lasted for an additional 7-8 hours. Several days later a repeated application of the same procedure gave the same results.

Complete relief of psoriatic arthritis pain by topical N-acetyl creatine ethyl ester (C15)

A 61 year old female with a 42 year history of psoriasis, and psoriatic arthritis for the past 8 years, was provided a topical solution of C15 4% in WP 82. Application of the solution to painful joints of the wrists, hands, fingers and ankles provided almost instant, complete relief of pain that lasted for 6-24 hours. She has used topical formulations of C15 for over 12 weeks, comparing efficacy of 2%, 3.5% and 5% concentrations of C15. She has found that the most effective of the three has been 5% which has repeatedly provided complete pain relief for up to 24 hours.

Ankle sprain pain completely relieved with topical N-acetyl creatine ethyl ester (C15)

A 58 year old female sprained her left ankle while hiking. Pain became disabling overnight. She was provided a solution of C15 4% dissolved in WP 82 which she applied to the ankle 2-3 times daily for 4-5 days which completely relieved the pain. Treatment was discontinued when pain did not recur.

Instantaneous complete relief of pharyngitis by spray mist of aqueous N-acetyl creatine ethyl ester (C15)

A 59 year old female upon arising from bed in the morning was acutely aware of a severe sore throat. Clinical examination about 4 hours later revealed her to have a deeply erythematous pharyngitis but having no signs of bacterial infection. She was provided, in a 2 oz spray container, a 3% aqueous solution of C15 that she sprayed into her mouth toward the inflamed pharynx. She reported an immediate complete relief of pain, which lasted for about 30 minutes. Repeated spraying during the day was associated with longer pain free intervals. She reported that at 7 PM the last pain free interval had been 1 hour. Next morning the pharyngitis had improved, and the spray mist was used less and less frequently. After 3 days her throat felt and appeared normal.

Relief of post trauma pain by topical N-acetyl creatine ethyl ester (C15)

A 65 year old female professional associate was provided a 9% solution of C15 in WEP 532 for possible use against incidental pain. Several weeks later she sent by e-mail the following message:

"Yesterday I slammed the top of my hand accidentally against a door. That really hurt and I could barely move my hand. Started to ice it and then realized that I had decided to keep one bottle of the pain medicine here at the shore. Put the med on it and in a minute or two the pain went away. Like a miracle. Iced it after as I could tell a welt was forming. Again, at bedtime I put a little of the pain med on it in case the earlier application wore off and iced again as it was a bit swollen. Looked red and maybe a little

swollen this morning but no pain!"

Complete and durable relief of lower leg pain in child by topical N-acetyl creatine ethyl ester (C15)

An 8 year old boy complained of recurring "leg aches" in the upper tibia/knee region, symptoms compatible with Osgood Schlatter Disease or variant thereof. An adult female family member had in her possession a formulation of 3% C15 dissolved in a lotion made up by adding a sufficient amount of water to Hydrophilic Ointment USP, a formulation which she was using topically to relieve pain of osteoarthritis. This formulation was applied to upper tibia/knee region of the boy. Complete relief of his pain occurred within a minute or so and lasted. Three similar episodes over the next year occurred. Topical treatment with the same formulation gave the same relief.

Discussion

The foregoing reports of clinical experiences underscore the conclusion that the creatine derivative N-acetyl creatine ethyl ester applied transcutaneously at sites of pain cause rapid complete and durable relief of pain.

The rapid action of analgesic effect from topical applications of N-acetyl creatine ethyl ester (C15), suggests that analgesic effect is mediated through epidermal receptor molecule(s). Hypothetically such receptor molecule(s) most likely would be a large glycoprotein present at the nerve endings in the epidermis. We believe it is nearly the same situation as that of Endomorphin-2 derivatives [8].

The fact that N-acetyl creatine ethyl ester (C15), is more effective topically than creatine as an analgesic agent may be explained as follows: Creatine is an amphoteric substance which is both positively and negatively charged when in aqueous solution. Such amphoteric substance cannot readily penetrate the intact skin. On the other hand, N-acetyl creatine ethyl ester (C15) is not an amphoteric substance, and is in an optimal form which can readily penetrate into the skin.

We have synthesized numerous creatine derivatives including N-acetyl creatine, and creatine ethyl ester. N-acetyl creatine ethyl ester (C15) appears to be the most potent analgesic substance. The analgesic potency is proportionate to how tight the bonding is between the receptor glycoprotein and a creatine derivative,

i.e. the tighter bonding is more potent. We believe it is nearly the same situation as that of endomorphin-2 derivatives [9].

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Conflict of Interest

The authors declared no conflict of interest for this study.

References

1. Gualano B, Rawson ES, Candow DG, et al. (2016) Creatine supplementation in the aging population: effects on skeletal muscle, bone and brain. *Amino Acids* 48(8): pp. 1793-1805.
2. Chilibeck PD, Kaviani M, Candow DG, et al. (2017) Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. *Open Access J Sports Med* 8: pp. 213-226.
3. Mills S, Candow DG, Forbes SC, et al. (2020) Effects of Creatine Supplementation during Resistance Training Sessions in Physically Active Young Adults. *Nutrients* 12(6): p. 1880.
4. Rima KD, Ghaleb D, Beal MF (2002) Use of creatine or creatine analogs for the treatment of diseases of the nervous system. US2002/0161049 A1.
5. Rima KD, Ghaleb D (2004) Use of creatine or creatine analogs for the treatment of diseases of the nervous system. US2004/0102419 A1.
6. Rima KD (2005) Use of creatine or creatine compounds for skin preservation. US2005/0227996 A1.
7. Rima KD, Ghaleb D, Beal MF (2010) Use of creatine or creatine analogs for the treatment of diseases of the nervous system. US2010/0303840 A1.
8. Yu RJ, Scott EJV (2017) Endomorphin-2, Its related Tetrapeptide Derivatives, Topical Analgesic Effect for Instant Relief of Various Pains. *Br J Phar Med Res* 2: pp. 733-740.
9. Yu RJ, Scott EJV (2020) Endomorphin-2 Derivatives: Rapid Relief of Various Pains by Topical Administration or by Superficial Local Injection. *Clin Case Rep J* 1(5): pp. 1-4.